A STAT3 Gene Expression Signature in Gliomas is Associated with a Poor Prognosis

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Abstract: Gliomas frequently display constitutive activation of the transcription factor STAT3, a protein that is known to be able to mediate neoplastic transformation. STAT3 regulates genes that play a central role in cellular survival, proliferation, self-renewal, and invasion, and a cohort of STAT3 target genes have been found that are commonly coexpressed in human cancers. Thus, these genes likely subserve the transforming ability of constitutively activated STAT3. To determine whether the coordinated expression of STAT3 target genes is present in a subset of human gliomas, and whether this changes the biology of these tumors in patients, gene expression analysis was performed in four distinct human glioma data sets for which patient survival information was available. Coordinate expression of STAT3 targets was significantly associated with poor patient outcome in each data set. Specifically, patients with tumors displaying high expression of STAT3 targets had a shorter median survival time compared to patients whose tumors had low expression of STAT3 targets. These data suggest that constitutively activated STAT3 in gliomas can alter the biology of these tumors, and that development of targeted STAT3 inhibitors would likely be of particular benefit in treatment of this disease.

Keywords: brain tumors, signal transduction, gene expression, transcription factors

Introduction

Central nervous system malignancies remain among the most difficult tumors to treat, owing to both anatomic and biologic features. The intimate association with critical structures and the highly vascular and infiltrating nature of gliomas make complete surgical resection particularly difficult. Furthermore, these tumors often manifest an intrinsic resistance to cell death triggered by cytotoxic agents or radiotherapy. To enhance our approach to the treatment of this disease it would be valuable to understand the molecular abnormalities that underlie these tumors.

A number of mutations have been found to occur commonly in human gliomas (Holland, 2001; Maher, 2001). One recurrent finding is the activation of tyrosine kinases, particularly the epidermal growth factor (EGF) receptor. The EGF receptor may be constitutively activated as a result of overexpression or from structural mutations that render the catalytic domain continually activated (Bigner, 1990; Libermann, 1985). In addition, activation of the platelet-derived growth factor (PDGF) receptor can occur due to concomitant overexpression of both the receptor and the PDGF ligand (Guha, 1995). Another soluble factor that can promote mitogenesis of normal and malignant glial cells is interleukin (IL)-6 (Van Meir, 1990). IL-6 can display enhanced expression in human gliomas (Tchirkov, 2001) as well as murine models of glial tumors (Weissenberger, 2004). Although each of these soluble proteins can activate a number of signaling pathways, one transcription factor that plays a central role in transducing signals from EGF, PDGF, and IL-6 is STAT3 (Alvarez, 2006).

Under basal conditions, STAT3 is found in the cytoplasm. Once activated through phosphorylation of a unique carboxy-terminus tyrosine residue, STAT3 forms dimers, translocates to the nucleus, and binds to nine base pair sequences in the promoter regions of target genes thereby activating (or in some cases repressing) transcription (Darnell, 1997; Ihle, 1996). STAT3 targets include genes involved in cell cycle progression, survival, self-renewal, and invasion (Alvarez, 2005). Reflecting these physiological functions of STAT3 target genes, STAT3 has been found to be activated inappropriately in a

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